A Randomized Trial of Goal Directed vs Standard Fluid Therapy in Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy

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Abstract The use of adequate fluid therapy during cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) remains controversial. The aim of the study was to assess whether the use of fluid therapy protocol combined with goal-directed therapy (GDT) is associated with a significant change in morbidity, length of hospital stay, and mortality compared to standard fluid therapy. Patients American Society of Anesthesiologists (ASA) II–III undergoing CRS and HIPEC were randomized into two groups. The GDT group (N=38) received fluid therapy according to a protocol guided by monitored hemodynamic parameters. The control group (N=42) received standard fluid therapy. We evaluated incidence of major complications, total length of hospital stay, total amount of fluids administered, and mortality rate. The incidence of major abdominal complications was 10.5 % in GDT group and 38.1 % in the control group (P=0.005). The median duration of hospitalization was 19 days in GDT group and 29 days in the control group (P<0.0001). The mortality rate was zero in GDT group vs 9.5 % in the control group (P=0.12). GDT group received a significantly (P<0.0001) lower amount of fluid (5812±1244 ml) than the control group (8269±1452 ml), with a significantly (P<0.0001) lower volume of crystalloids (3884±1003 vs 68,528±1413 ml). In CRS and HIPEC, the use of a GDT improves outcome in terms of incidence of major abdominal and systemic postoperative complications and length of hospital stay, compared to standard fluid therapy protocol.

Keywords Chemotherapy · Fluid therapy · Postoperative complications · Randomized controlled trial · Regional perfusion

Introduction

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is indicated in primary and secondary peritoneal neoplasms. It consists of almost complete removal of the peritoneal surface, multiple visceral resections, a variable number of intestinal anastomoses, followed by perfusion of chemotherapy inside the abdominal cavity, for 90 min at 42 °C. The wide extent of surgical resection and physicochemical trauma of the HIPEC alters capillary permeability, resulting in tissue damage and facilitating abdominal and systemic complications with postoperative morbidity and mortality ranging from 22 to 41 % and from 2 to 5 % respectively, with a significant increase in hospitalization time. Proper management of perioperative fluid therapy during CRS and HIPEC remains controversial. Permissive infusion regimen was proposed in the past to counteract fluid, blood, and protein losses; however, it excessively exposes the patient to the risk of fluid overload, tissue edema, and severe abdominal complications. On the other hand, the use of restrictive infusional regimens may expose the patient to hemodynamic...
instability, determining tissue hypoperfusion, organ damage, and worsen the nephrotoxic chemotherapy drug effect. Clinical evidence suggests that goal-directed fluid therapy (GDT) is associated with a significant reduction of intestinal and systemic complications and improvement of prognosis in major abdominal surgery.\textsuperscript{7,12} The aim of our study was to assess whether the use of a protocol of fluid therapy combined with GDT may be associated with a significant change in outcome, compared to standard fluid therapy protocol. The primary endpoint was the incidence of major abdominal complications (anastomotic dehiscence, enteric fistulae, intestinal perforation, abdominal abscesses); secondary endpoints consisted in the incidence of systemic complications, duration of hospital stay, and mortality.

**Materials and Methods**

The study was approved by the ethics committee of the Regina Elena National Cancer Institute, Rome, Italy, with registration number 89/10; the procedures followed were in accordance with the Declaration of Helsinki 1975, revised Hong Kong 1989. After having obtained the written informed consent, all consecutive ASA II–III patients with peritoneal carcinomatosis, candidates for peritoneectomy and HIPEC, who met the inclusion criteria, were enrolled in the period between June 2010 and September 2012. Patients under the age of 18 and patients with hemodynamically significant aortic regurgitation and heart rhythm disorders were excluded from the study. This is a single-center, prospective, randomized study. An operator who is not directly involved in the study randomly divided patients into two treatment groups. This process of randomization was carried out according to specific dedicated software, developed in-house, by GW Basic programmer, which generated an assignment code verified immediately before inducing anesthesia. A blinded observer recorded the outcomes. One group received fluid therapy according to therapy targeted at optimizing monitored hemodynamic parameters (GDT group); the other group received fluid therapy (control group) in accordance with a standardized protocol. In the GDT group, the target was identified in maintaining the minimum cardiac index (CI) threshold value, assessed using the FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA, USA, software version 1.14) was applied in all patients in order to continuously monitor CI, indexed stroke volume (SVI), and stroke volume variation (SVV). The CI was maintained at values greater than or equal to 2.5 l/min/m\(^2\). Fluid therapy protocol was mainly restrictive, involving basal infusion of crystalloids at 4 ml/kg/hour.\textsuperscript{78} Mean arterial pressure (MAP) was maintained at values between 65 and 95 mmHg. It was possible to administer boluses of colloids (hydroxyethyl starch (HES) 130/0.4) of 250 ml in 15 min and infuse inotropic agents (dopamine) if CVP was ≤35 ml/m\(^2\), and SVV>15 %. In the case of CI<2.5 l/min/m\(^2\) and SVI<35 ml/m\(^2\) with SVV<15 %, an infusion with dopamine was initiated (Fig. 1).

In the GDT group, the FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA, USA, software version 1.14) was applied in all patients in order to continuously monitor CI, indexed stroke volume (SVI), and stroke volume variation (SVV). The CI was maintained at values greater than or equal to 2.5 l/min/m\(^2\). Fluid therapy protocol was mainly restrictive, involving basal infusion of crystalloids at 4 ml/kg/h and boluses of colloids (HES 130/0.4) of Cl<2.5 l/min/m\(^2\), SVI<35 ml/m\(^2\), and SVV>15 %. In the case of CI<2.5 l/min/m\(^2\) and SVI<35 ml/m\(^2\) with SVV<15 %, an infusion with dopamine was initiated (Fig. 1).

In both groups, patients were transfused with concentrated red cells for Hb values <8 mg/dl (9 mg/dl in patients with congestive heart failure or coronary heart disease). In both groups during the HIPEC (duration 90 min), fresh frozen plasma (FFP) was administered (1 U/15 min) for a total of...
six units, in accordance with the standardized technique applied at our institute. Diuresis was maintained at values equal to or greater than 120 ml/15 min; the administration of diuretics (furosemide) was free up to a maximum of 250 mg.

At the end of the operation, patients were extubated in the operating theater and transported to the intensive care unit (ICU), where depending on their clinical conditions whether stable and normal, returned to their original hospital ward. In the postoperative period, the same standardized regimen of fluid therapy was applied to both groups: Infusion solutions through total parenteral nutrition (TPN) up to 3000 ml/day was administered and gradually converted into enteral nutrition (EN) after 5–7 days, starting 10 ml/h to achieve the dose of 60 ml/h, until mouth feeding resumed.

The main hemodynamic parameters were recorded in all patients at different times (T0: induced anesthesia; T1: 30 min from the beginning of HIPEC, T2: 30 min after the end of surgery) (ABP, HR, SpO2, hourly diuresis). In the GDT group, the CI, SVI, and SVV were measured. At the end of surgery, readings in both groups were taken of the total amount of fluids administered, their breakdown (crystalloid/colloid), the total number of colloid boluses administered, and the use of diuretics and inotropic agents.

In both groups, we evaluated the incidence of major abdominal and systemic complications that occurred within 30 days, as well as the total duration of hospital stay and mortality up to 30 days. The incidence of postoperative complications was rated by anesthesiologists who were not involved in the intraoperative management of patients. The major abdominal complications were anastomotic leakage, enteric fistulas, perforation, and abdominal abscesses (confirmed by computerized tomography); systemic complications were divided into cardiac (electrocardiographic signs or laboratory data of myocardial infarction, angina, or arrhythmia), hepatic (persistent alteration in hepatic function tests including bilirubin, prothrombin time, ammonia concentration, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase), respiratory (X-ray findings of airspace or interstitial opacity, lobar consolidation, or pleural effusions; severe respiratory failure requiring respiratory support), and renal (oliguria with urine output<0.5 ml/kg/h for more than 4 h, creatinine increase>30 % of preoperative values, dialysis). Furthermore, the incidence of readmission to the ICU was also assessed.

Statistical Analysis

The study was designed as a two-arm parallel prospective, randomized trial. The primary endpoint of the study was the occurrence rate of abdominal complications (dehiscence of anastomosis, intestinal perforation, abdominal abscesses). The number of patients required for the study was determined by assuming that in the standard arm, the rate of abdominal complications was equal to 40 % and assuming that GDT could reduce this by 30 % in absolute value, setting the significance level to 5 % and the power to 80 %. A sample size of 80 patients was identified. The analysis was carried out on the population “per protocol”. The Fisher’s exact test was used to assess the primary endpoint and measure the association between categorical variables. Once the assumption of normality with the Kolmogorov-Smirnov test was verified, the continuous variables were compared using the Student’s t test. The Kaplan-Meier method was used to estimate the duration of hospitalization, and the difference between the two curves was evaluated by the log-rank test. All P values
were two-sided. IBM SPSS Statistics version 20.0 was used to implement the statistical analyses.

Results

The flowchart of the patients who participated in the study is shown in Fig. 2. Eighty patients in total were randomized: 42 patients were assigned to the control group and 38 to the GDT group. The groups were similar in age, sex, weight, comorbidity, type and duration of surgery, ASA classification, and cancer type (Table 1). The intraoperative hemodynamic data recorded is shown in Table 2. The incidence of major abdominal complications in the experimental group was 10.5 % (95 % CI: 4.1–24.1) and significantly lower than that of the control group, which was equal to 38.1 % (P=0.005, 95 % CI: 25.0–53.2), with an absolute risk reduction of 27.6 % (95 % CI: 8.7–43.9). The median duration of hospitalization was 29 days (95 % CI: 25–33) in the control group and 19 days (95 % CI: 17–21) in the GDT group (P<0.0001, log-rank test) (Fig. 2). The mortality was 4 out of 42 patients (9.5 %, 95 % CI: 3.8–22.1), in the control group (3 patients developed multiple organ dysfunction syndrome (MODS) resulting from abdominal abscess; 1 patient had MODS resulting from anastomotic leakage), and no deaths occurred in the GDT group (P=0.12). The number of patients who developed at least one complication in the postoperative period was significantly lower (P<0.0001) in the GDT group (10 in 38 patients; 26.3 %, 95 % CI: 15.0–42.0) compared to the control group (39 in 42; 92.9 %, 95 % CI: 81.0–97.5). The incidence of specific systemic complications in the two groups is shown in Table 3. The incidence of readmission to the ICU was 11.9 % (95 % CI: 81.0–97.5) in the control group and 0 % in the GDT group (P<0.0001). There were no significant differences in urine output, blood loss, and number of patients receiving red blood cells or inotropes (Table 3).

Discussion

In our study, GDT was confirmed as an effective method for reducing the length of hospital stay and postoperative complications in patients undergoing CRS and HIPEC compared to conventional fluid therapy treatment, as reported in previous experiences in traditional surgery. Moreover, the mortality rate decreased and is not considered statistically significant. In CRS with HIPEC extensive surgical trauma, important exposure of the viscera and long duration of the procedure may grow to a considerable size and predispose the patient to a state of hypovolemia and hemodynamic instability during the subsequent phase of the HIPEC. Furthermore, the administration of potential nephrotoxic chemotherapeutic drugs imposes the need to adopt adequate strategies of renal protection, avoiding dehydration. However, CRS and HIPEC procedure

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Fig. 2  Patient flow throughout the study. HIPEC hypertermic intraperitoneal chemotherapy.

*Supervening change in heart rate (sustained sinus tachycardia) which has required use of cardioactive drugs not covered by the protocol

**Supervening change in heart rate (prolonged bradycardia) which has required use of cardioactive drugs not covered by the protocol
determines important and sometimes conflicting pathophysiological dynamics; the limit between hypovolemia and hypervolemia is very subtle and may change during surgery. Tissues, in fact, are due to prolonged mechanical, thermal, and chemical damage associated with the procedure and are consequently particularly prone to developing interstitial edema, even in hypovolemic conditions.

Under these circumstances, proper management of balancing fluid plays a critical role through maintaining optimal blood volume during the different phases in order to ensure an adequate supply of oxygen to the tissues,\textsuperscript{14} while avoiding states of over hydration.

In our study, the CI was used as a target for the GDT. Although the oxygen delivery index (DO\textsubscript{2}I) is, according to many authors, the reference target, its determination requires a calculation obtained through repeated blood gas sampling and cannot be easily applied during surgery. The FloTrac/Vigileo system allows the continuous determination of cardiac output by analyzing the wave morphology of the arterial pulse, and its easy use is particularly indicated in the operating room. The continuous detection of CI can be considered a valid surrogate of the DO\textsubscript{2}I, and its use as a hemodynamic target constitutes a valid alternative, in combination with occasional appropriate sample of hemoglobin values and arterial saturation.

A CI of 2.5 l/min/m\textsuperscript{2}, the minimum threshold value to ensure an adequate supply of oxygen to the tissues, is a conceptually different approach from what was originally proposed by Shoemaker and subsequently developed by many other authors who have used the predetermined over limit hemodynamic values of CI and DO\textsubscript{2}I as a therapeutic target.\textsuperscript{15}

A GDT based on the pursuit of predetermined over limit hemodynamic values can in some circumstances be ineffective, if not harmful. It is therefore necessary to customize the GDT by identifying reference hemodynamic parameters based on the hemodynamic ability of the patient and the operating context.\textsuperscript{16} A GDT based on achieving over limit DO\textsubscript{2}I, CI, or SVI values in CRS and HIPEC operations necessarily involves the infusion of large quantities of liquids or the administration of high doses of inotropes, thus exposing patients to the risk of an overload in fluids or abnormal rhythms that are difficult to sustain.

Our findings show a reduction in mortality and impressive absolute reductions in complications and hospital length of stay in intervention group. The GDT group was managed by personalized treatment protocols adapted to the type of surgery; the hemodynamic variations were recorded in real time, allowing action to be taken before the resulting tissue alterations. In control group, although there were predefined

<table>
<thead>
<tr>
<th>Variable</th>
<th>GDT group (N=38)</th>
<th>Control group (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)—mean (SD)</td>
<td>54.5 (9.8)</td>
<td>57.6 (8.8)</td>
</tr>
<tr>
<td>Gender male—number (%)</td>
<td>22 (57.8)</td>
<td>31 (73.8)</td>
</tr>
<tr>
<td>Weight (kg)—mean (SD)</td>
<td>71.7 (13.8)</td>
<td>69.1 (17.4)</td>
</tr>
<tr>
<td>BMI—mean (SD)</td>
<td>25.6 (4.2)</td>
<td>25.4 (4.7)</td>
</tr>
<tr>
<td>ASA score III—number (%)</td>
<td>4 (10.5)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Hypertension—number (%)</td>
<td>19 (50)</td>
<td>17 (40.5)</td>
</tr>
<tr>
<td>Cardiac failure—number (%)</td>
<td>2 (5.3)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Diabetes—number (%)</td>
<td>7 (18.4)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>COPD—number (%)</td>
<td>0 (0)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Length of operation (hours)—mean (SD)</td>
<td>9.3 (1.5)</td>
<td>9.7 (1.2)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)—mean (SD)</td>
<td>12.9 (1.9)</td>
<td>13.1 (2.1)</td>
</tr>
<tr>
<td>Hematocrit (%)—mean (SD)</td>
<td>37.5 (4.7)</td>
<td>38.2 (5.1)</td>
</tr>
<tr>
<td>Albumin (g/dl)—mean (SD)</td>
<td>3.6 (0.4)</td>
<td>3.5 (0.3)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)—mean (SD)</td>
<td>0.87 (0.35)</td>
<td>0.89 (0.38)</td>
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<tr>
<td>Cancer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Rectum</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Appendix</td>
<td>5</td>
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<tr>
<td>Stomach</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ovary</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

\textit{ASA} American Society of Anesthesiologists, \textit{GDT} goal-directed therapy, \textit{BMI} body mass index, \textit{SD} standard deviation, \textit{COPD} chronic obstructive pulmonary disease

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
Variable & GDT group (N=38) & Control group (N=42) \\
\hline
Heart rate (bpm) & & \\
T0—Baseline & 76 (4.8) & 76 (5.3) & 0.80 \\
T1—During HIPEC & 109 (8.2) & 110 (10.4) & 0.62 \\
T2—End of surgery & 81 (6.4) & 81 (4.6) & 0.78 \\
\hline
MAP (mmHg) & & \\
T0—Baseline & 76.9 (6.1) & 77.1 (5.3) & 0.87 \\
T1—During HIPEC & 91.7 (6.9) & 91.1 (5.1) & 0.68 \\
T2—End of surgery & 74.8 (3.5) & 77.9 (6.5) & 0.008 \\
\hline
SVI (ml/min/m\textsuperscript{2}) & & \\
T0—Baseline & 44.8 (8.9) & & \\
T1—During HIPEC & 43.4 (9.9) & & \\
T2—End of surgery & 45.7 (6.7) & & \\
\hline
CI (ml/min/m\textsuperscript{2}) & & \\
T0—Baseline & 3.4 (0.5) & & \\
T1—During HIPEC & 4.6 (0.5) & & \\
T2—End of surgery & 3.7 (0.4) & & \\
\hline
\end{tabular}
\caption{Intraoperative hemodynamic parameters}
\end{table}
Intraoperative volume replacement

<table>
<thead>
<tr>
<th>Variable</th>
<th>GDT group (N=42)</th>
<th>Control group (N=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalloid volume replacement</td>
<td>3884 (1003)</td>
<td>6852 (1413)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Colloid volume replacement (ml)</td>
<td>1927 (318)</td>
<td>1417 (279)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Total volume replacement (ml)</td>
<td>5812 (1244)</td>
<td>8269 (1452)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Crystalloid volume infused (ml/kg/h)</td>
<td>5.67 (0.5)</td>
<td>10.18 (1.5)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Colloid volume infused (ml/kg/h)</td>
<td>3.11 (0.6)</td>
<td>2.22 (0.6)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Total volume infused (ml/kg/h)</td>
<td>8.54 (1.1)</td>
<td>12.30 (1.6)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

All data are expressed as mean (standard deviation). GDT goal-directed therapy

*Significant
surgical, thermal, and chemical stress prepares for tissue edema as well as small fluid overloads. We therefore felt that the identification of a SVV threshold for the colloid bolus infusion that was slightly higher than that identified in similar experiences was appropriate, which protects the patient from the risk of relative hypovolemia. Maintaining adequate CI values, even under conditions of moderate water restriction, can be obtained alternatively by administering moderate doses of inotrope.

Our experience agrees with the results of other studies that correlate GDT using colloids with a lower incidence of postoperative complications (especially bowel) in high-risk patients undergoing major abdominal surgery. In fact during peritonectomy and HIPEC, it is particularly important to maintain a good oncotic pressure due to the massive loss of protein due to the surgical procedure. We must consider that colloids allow a volume replacement of about 90%, while the increase of intravascular volume of crystalloids is less of 20%. This can contribute to interstitial edema with damage to the renal tubular cells, so the renal damage may be greater for hypovolemia, tissue hypoxia, or cellular edema rather than to the administration of colloids. At present, it is difficult to establish whether a beneficial effect of colloid exists (systemic effects of the improvement in the patient’s hemodynamic profile, effects on the regional intestinal flow, or a combination of both), especially considering the controversial events related to the regulation of the use of HES in Europe. However, after a precautionary ban on the use, the European Community concluded the risk-benefit ratio favorable for HES in the treatment of acute hypovolemia, giving specific contraindications. Limitations in our study were the sample size and the lack of blinding for operating team.

Conclusion

In patients undergoing peritonectomy with HIPEC, the use of a restrictive fluid therapy regimen combined with a GDT aimed at maintaining the minimum threshold of CI greater than or equal to 2.5 l/min/m² improves outcome in terms of the incidence of major abdominal and systemic postoperative complications and length of stay compared to a standard fluid therapy protocol; the incidence of mortality is decreased and is not statistically significant.

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Conflict of Interest The authors declare that there is no conflict of interest.

References


33. Kimberger O: Goal directed colloid administration improves the microcirculation of healthy and perianastomotic colon. *Anesthesiology* 2009; 110:496-450